Metabolism of Other Hexoses

By

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INTENDED LEARNING OBJECTIVES (ILOs)

By the end of this lecture the student will be able to:

1. **Identify different metabolic pathways of fructose metabolism**
2. **Relate abnormal fructose metabolism to clinical disorders**
3. **Corelate abnormal galactose metabolism to clinical disorders**

Case presentation

A 10 month old boy who initially appears healthy began to develop vomiting, abdominal pain and hypoglycemia

Case presentation

History revealed that these symptoms began after fruit juices were introduced to his diet as he was being weaned off breast milk

Physical examination: was remarkable for hepatomegaly & Jaundice

Lab investigations including fructose tolerance test revealed that:

- **Blood glucose level: 60 mg/dl especially after intake of fructose or sucrose.**
- **The test for reducing sugar in urine was positive.**
- **AST and ALT levels were elevated.**
- **Pi concentrations decreased by 50%.**
- **Lactate & uric acid levels were elevated.**
- **Enzyme assay : Decreased Aldolase-B activity**

Diet Recommendations:

Complete elimination of all sources of sucrose, fructose, and sorbitol from the diet.

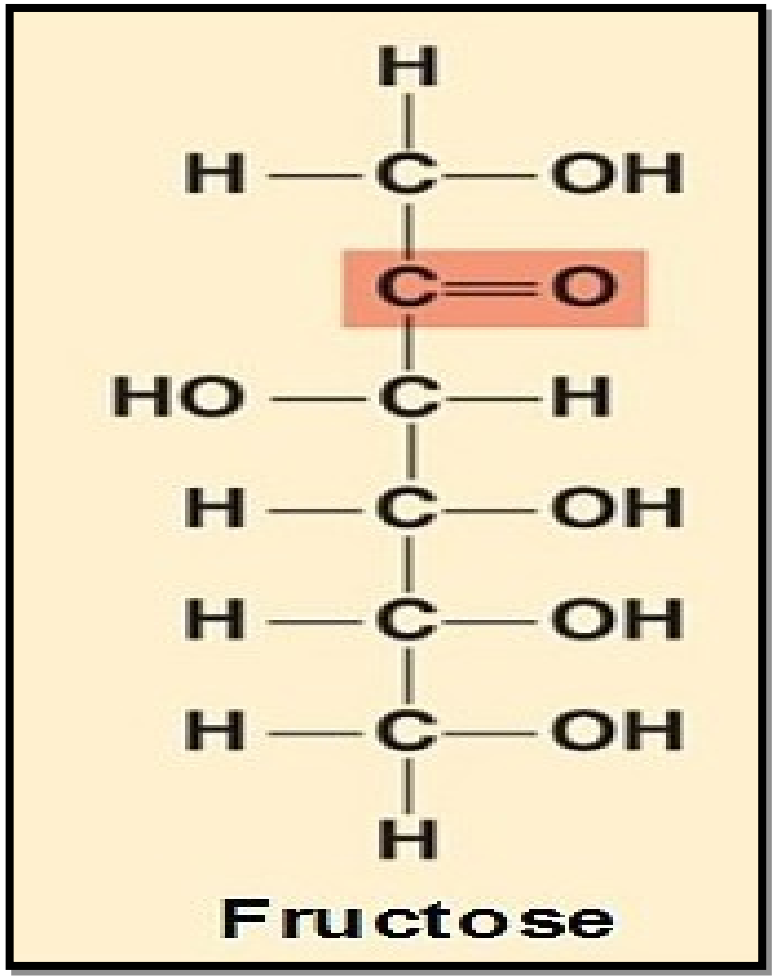
What is the most likely diagnosis of this case ?

Hereditary Fructose intolerance (Fructose induced hypoglycemia).

which is an inborn error of fructose metabolism

What Is Fructose?

A Monosaccharide (ketohexose) that occurs in significant amounts in diet (1ry in disaccharides)



Sources Of Fructose

1- Disaccharide sucrose: (major source) , cleaved in the intestine, releases fructose & glucose.

2- Found as a Free monosaccharide:

- **Fruits**
- **Honey**
- **High-fructose corn Syrup (55% fructose/45% glucose typically), which is used to sweeten Soft drinks & many foods.**

Sources Of Fructose

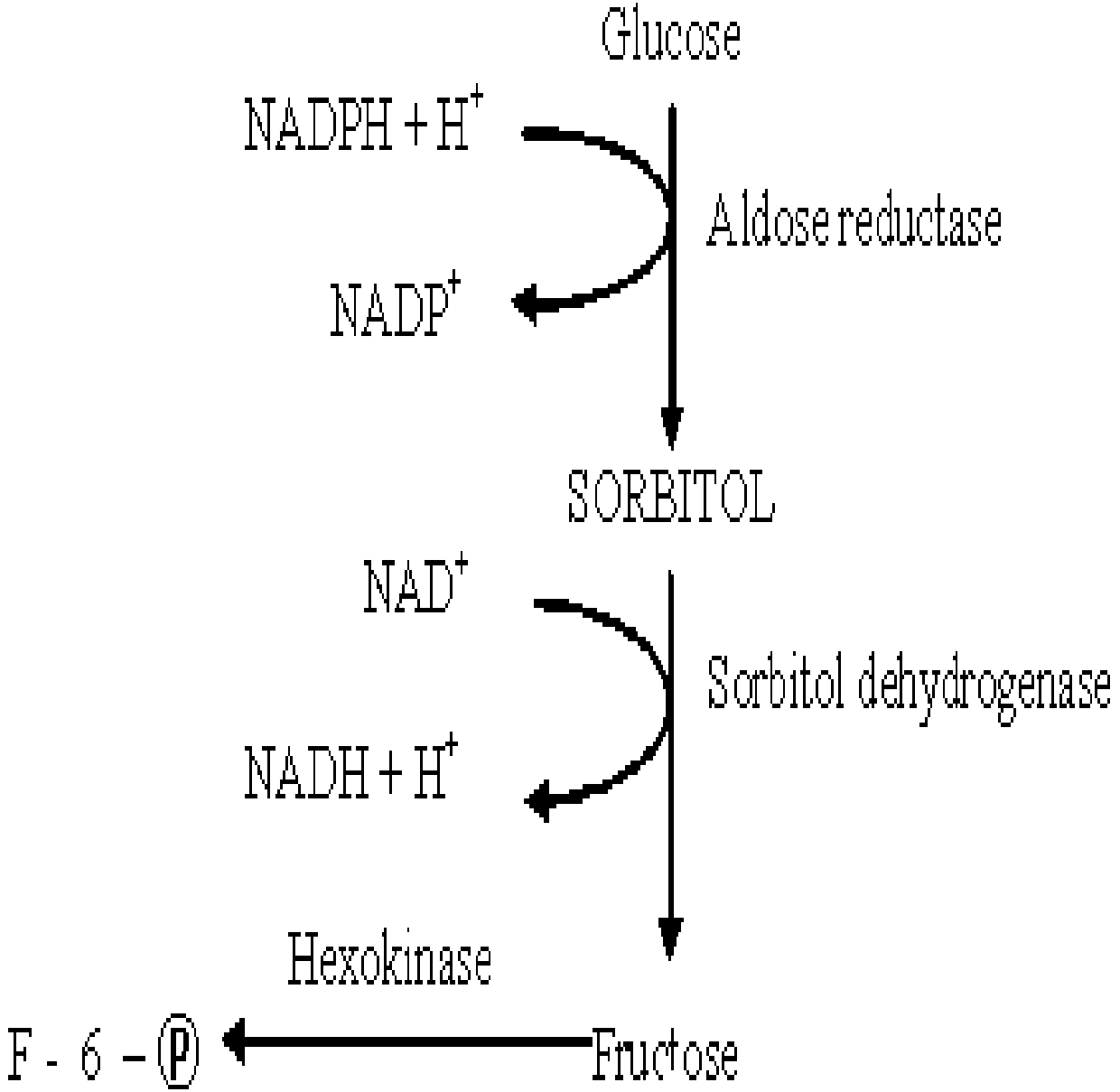
3- Fructose can arise from glucose inside the body via sorbitol (polyol) pathway in some tissues.

Organs can that utilize fructose:

Liver, Kidney, intestinal mucosa, seminal vesicles, adipose tissue, Skeletal muscle but not brain.

Sorbitol (polyol) pathway

- **The energy for mobility of sperm is mainly derived from fructose**



Fructose to enter the pathways of intermediary metabolism, it

must first be phosphorylated

Fructokinase

- Has very high affinity (low Km), for fructose.

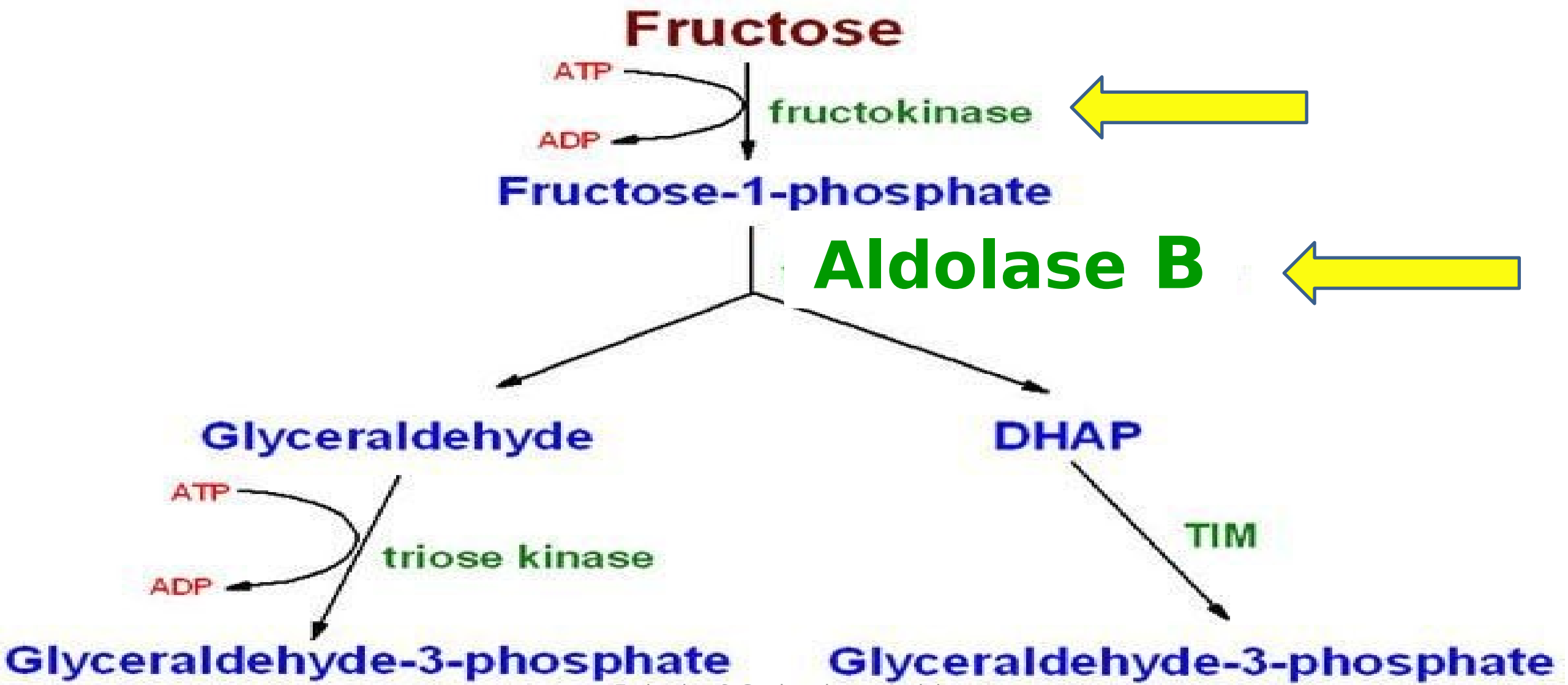
- It provides 1ry mechanism for fructose phosphorylation.

- Found in the liver (which processes most of dietary fructose), kidney& SI mucosa.

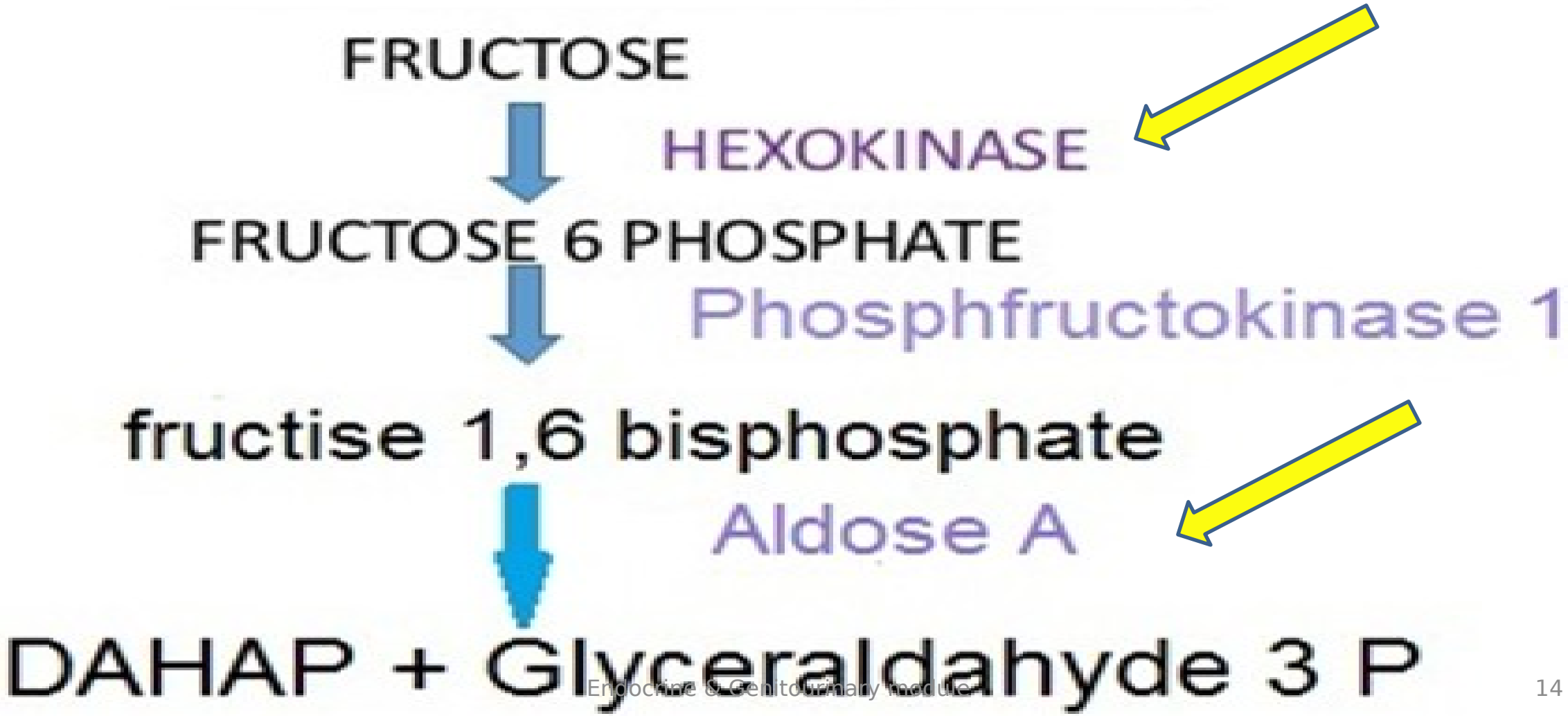
Hexokinase

has a very low affinity (high Km), for fructose _

A) In the liver, kidney, and intestine:



B) In other tissues such as muscle and adipose



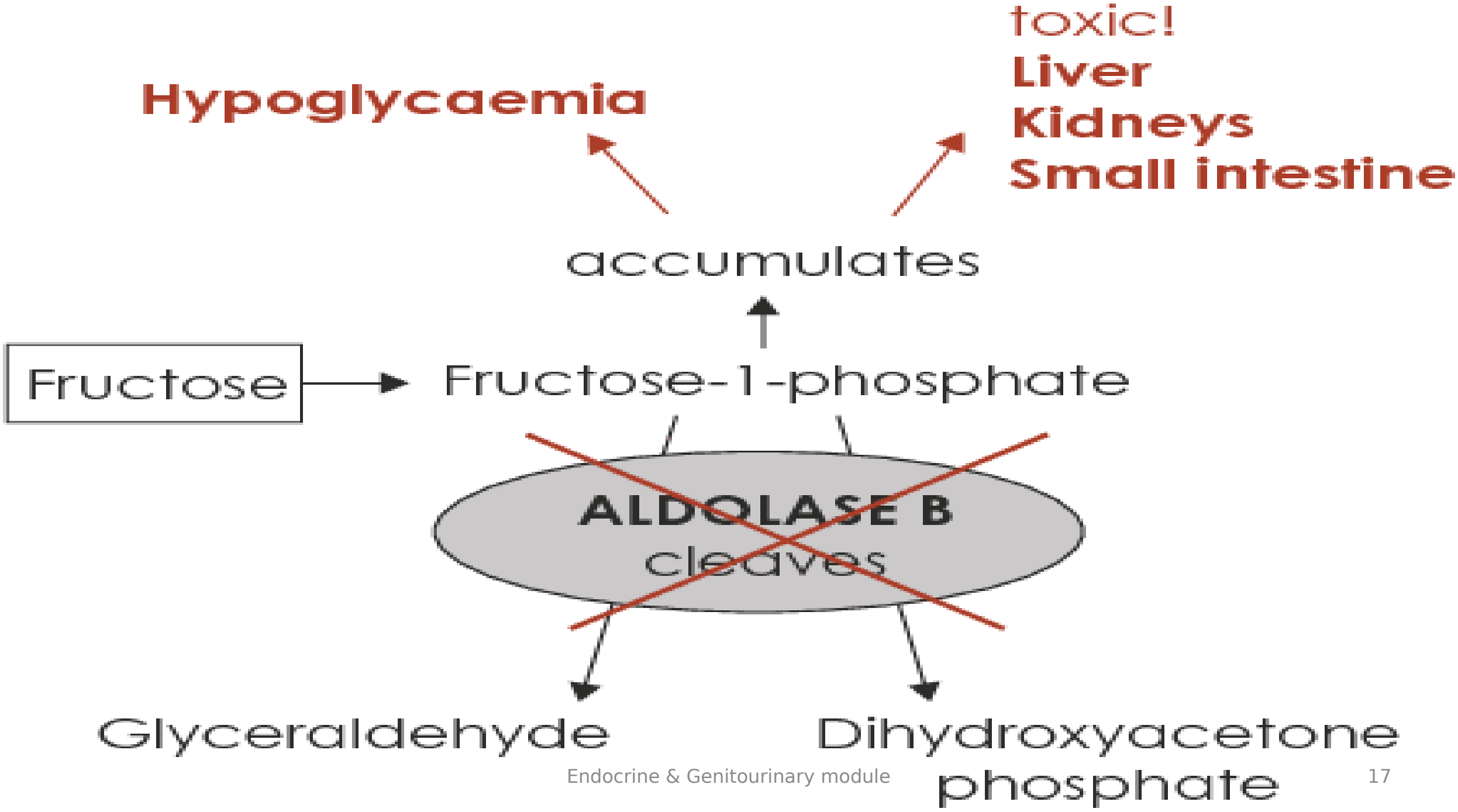
HEREDITARY FRUCTOSE INTOLERANCE

Hereditary Fructose Intolerance (Fructose induced hypoglycemia)

- **Inborn error of fructose metabolism.**

- **It is an autosomal recessive disease caused by mutation in the gene encoding Aldolase B enzyme.**

- **Symptoms & signs appear when a baby is weaned & begins to be fed on food containing fructose or sucrose.**


Hypoglycaemia
toxic!
Liver
Kidneys
Small intestine
accumulates
Fructose
Fructose-1-phosphate
ALDOLASE B
cleaves
Glyceraldehyde
Dihydroxyacetone
phosphate

Clinical picture of HFI

1- Hypoglycemia: due to inhibition of glycogenolysis & g ogenesis

WHY??

2- Liver: ⟹ **Hepatomegaly due to accumulation of F-1-P** ⟹

⟹ **Liver cell failure**

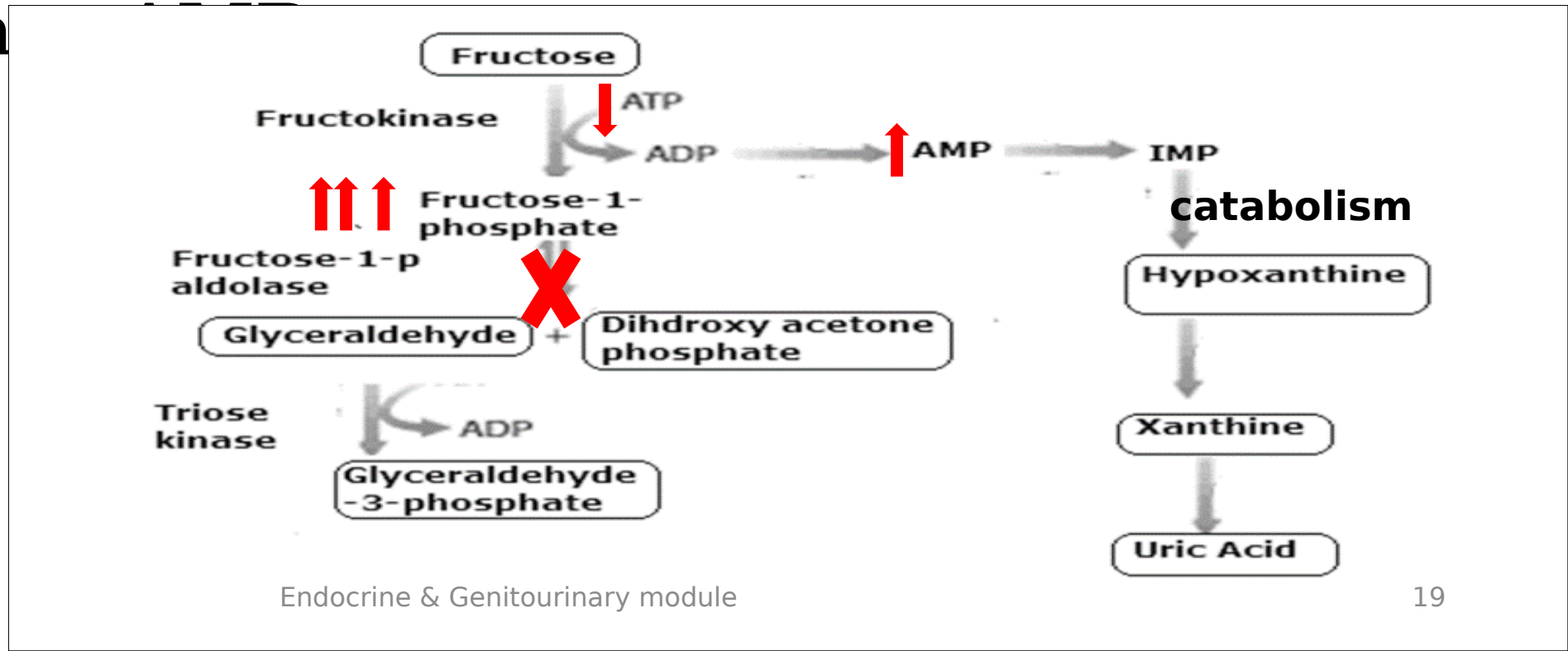
Jaundice d.t defective bilirubin conjugation

3- Lactic acidosis: due to defective gluconeogenesis

Symptoms of HFI?

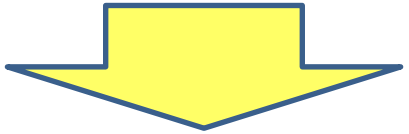
4- Renal dysfunction: due to toxic accumulation of F-1-P

5- Hyperuricemia: due to lactic acidosis, decrease ATP & increa

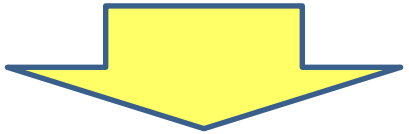


Hereditary fructose intolerance causes hypoglycemia, why?

Defect in the aldolase B enzyme



Fructose 1-phosphate accumulates in the hepatocytes



Trap phosphate in the liver and inorganic phosphate (Pi) decreased

Decreased inorganic phosphate (Pi)

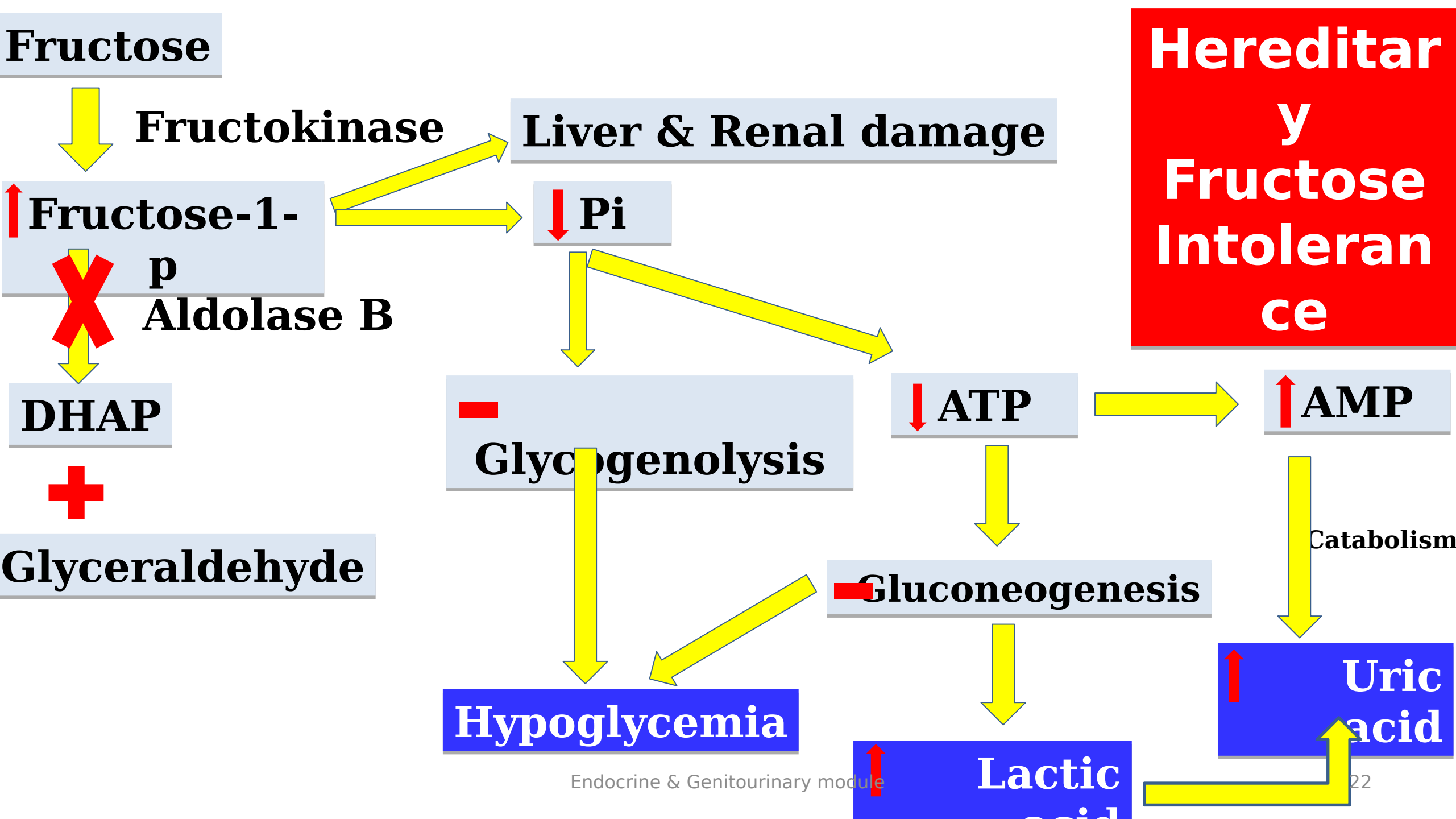
Inhibit glycogen phosphorylase which is required to break glycogen into glucose-6-phosphate

(Inhibit glycogenolysis)

Decrease ATP & increase AMP

(Inhibit gluconeogenesis)

Hypoglycemia


Fructose
Fructokinase
Liver & Renal damage
Hereditary Fructose Intolerance
Fructose-1-p
Aldolase B
Pi
DHAP
Glyceraldehyde
Glycogenolysis
ATP
AMP
Catabolism
Gluconeogenesis
Hypoglycemia
Uric acid
Lactic

Diagnosis of HFI is made on the basis of:

- **Fructose in the urine**
- **Enzyme assay using liver cells**
- **DNA-based testing**

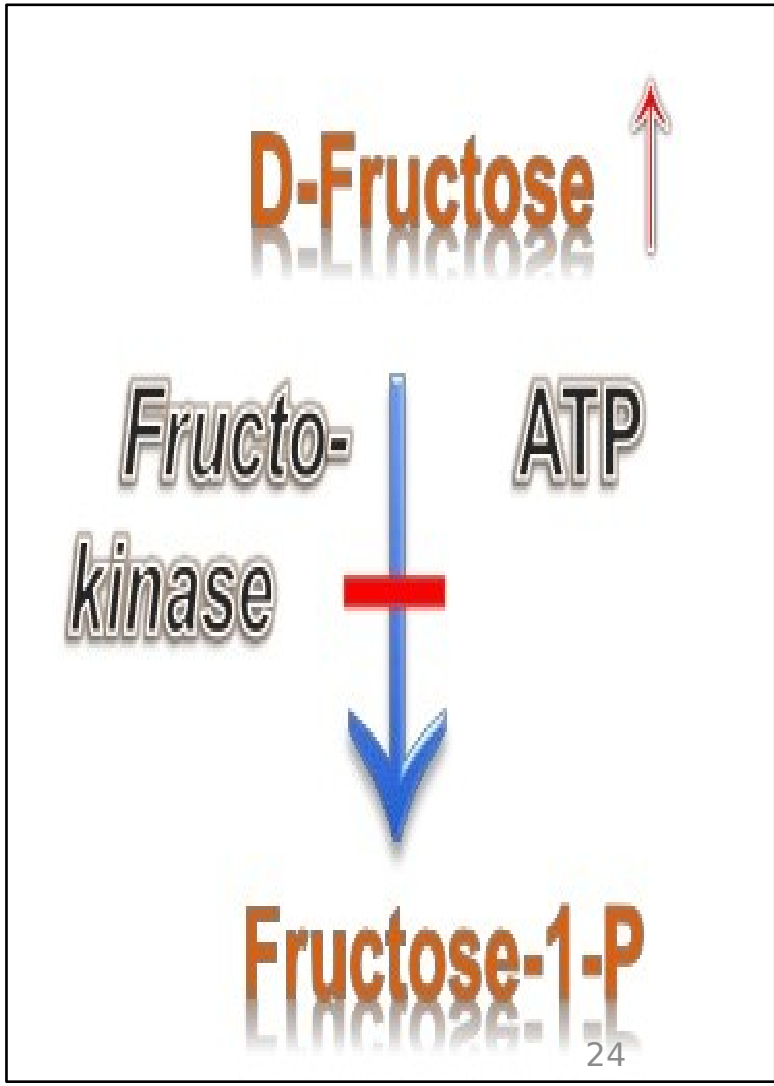
Treatment of HFI:

- **Sucrose as well as fructose, must be removed from the diet to prevent liver failure & possible death.**

Essential Fructosuria

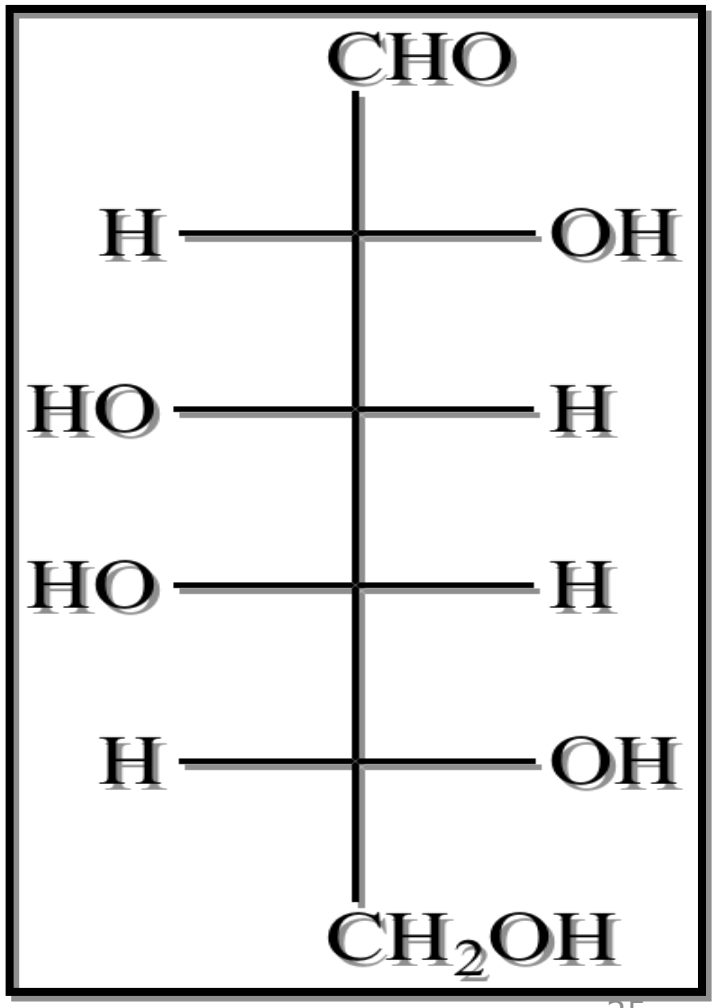
Autosomal recessive disorder (1:130,000)

- **Caused by a deficiency of the hepatic fructokinase enzyme, fructose is not metabolized in the liver**
- **Fructose is either excreted unchanged in the urine or metabolized to F-6-P by hexokinase in adipose tissue and muscles**
- **Clinically benign condition with no clinical symptoms**
- **No treatment is indicated**



What is Galactose?

Another Monosaccharide (hexose) that occurs in significant amounts in diet (1ry in disaccharides)

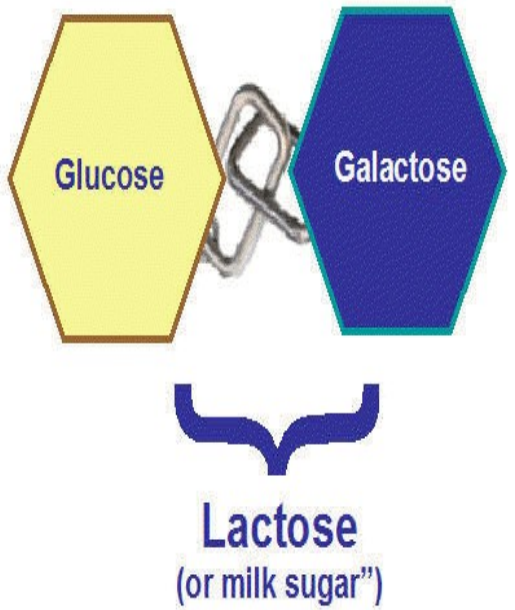


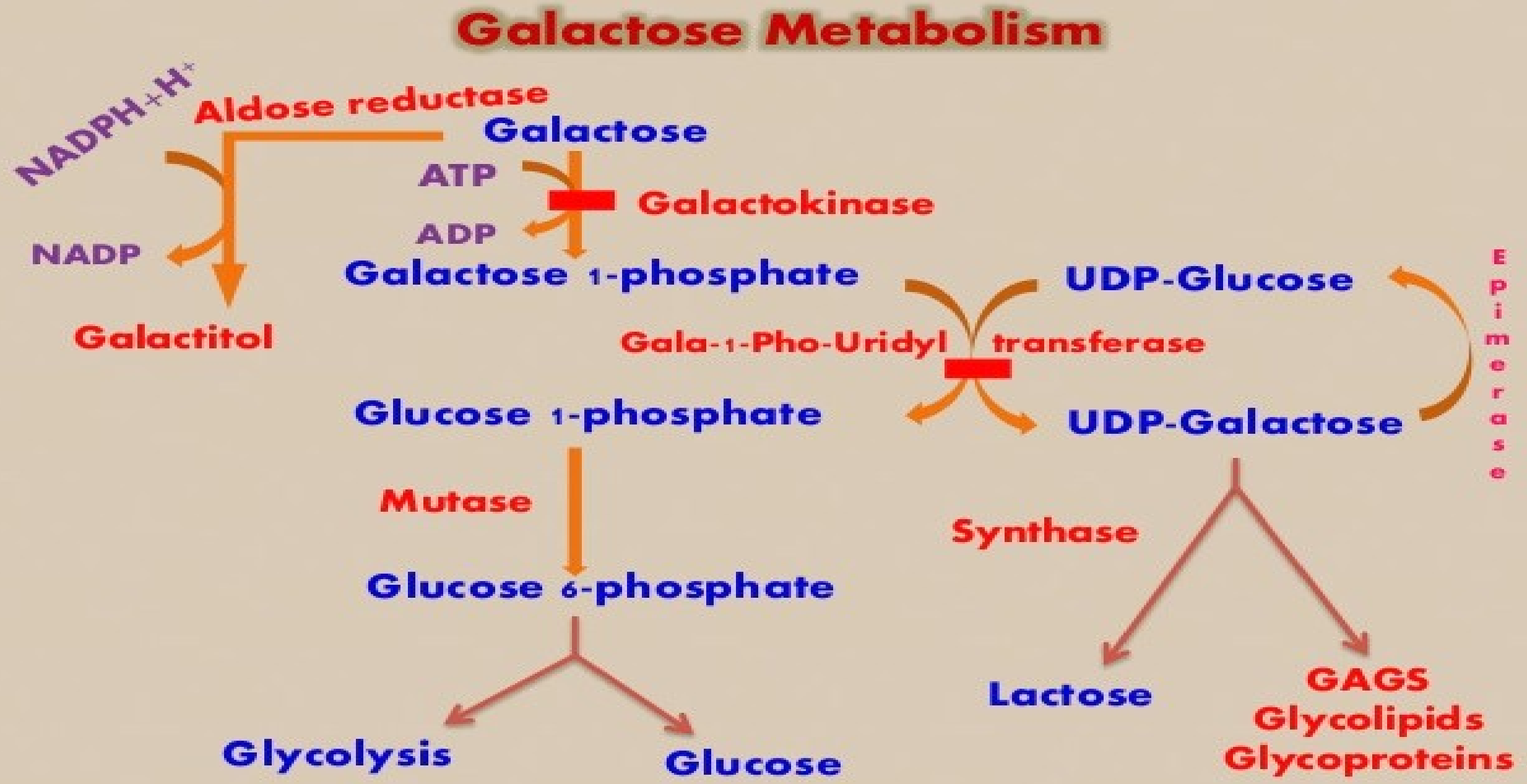
Sources of Galactose

- **Major dietary source of galactose is obtained from milk & milk products (digestion of lactose by lactase in SI yield glucose & galactose)**

- **Some galactose can also be obtained by lysosomal degradation of complex carbohydrates (glycoproteins & glycolipids)**

Galactosyl β(1→4)-glucose



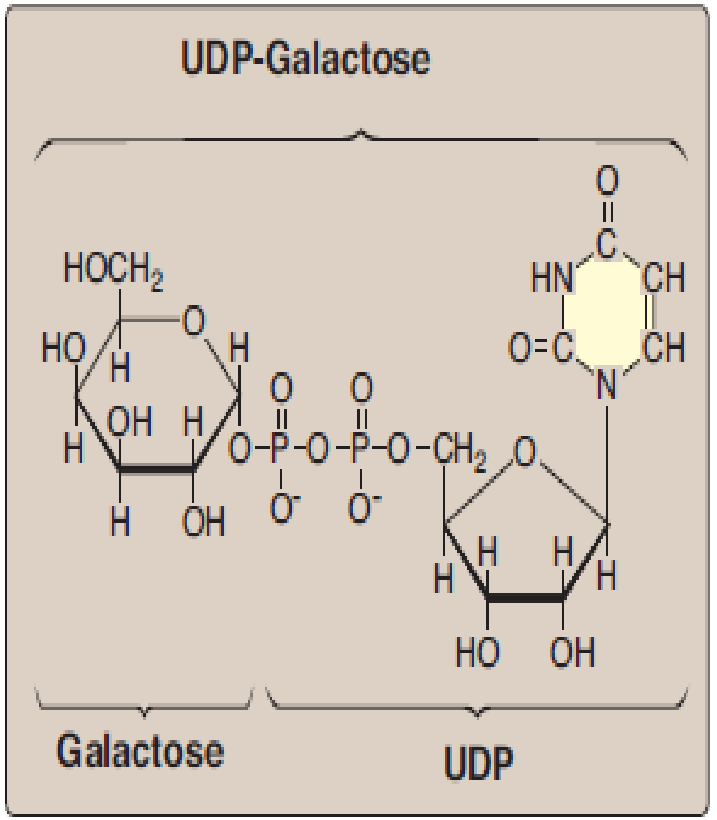

Galactose Metabolism
NADPH+H+
Aldose reductase
Galactose
ATP
Galactokinase
ADP
NADP
Galactose 1-phosphate
UDP-Glucose
Epimerase
Galactitol
Gala-1-Pho-Uridyl transferase
Glucose 1-phosphate
UDP-Galactose
Mutase
Synthase
Glucose 6-phosphate
Lactose
GAGS
Glycolipids
Glycoproteins
Glycolysis
Glucose

Galactose Metabolism

- **Galactose must be phosphorylated before it can be further metabolized.**
- **This occurs in most tissues by galactokinase enzyme producing galactose 1-phosphate .**
- **Galactose 1-phosphate is first converted to UDP-galactose.**
- **This occurs in an exchange reaction, in which UDP-glucose reacts with galactose 1-phosphate, producing UDP galactose and glucose 1-phosphate.**
- **This is catalyzed by galactose 1-phosphate uridyl transferase (GALT) enzyme.**

Role of UDP-galactose

UDP-galactose serve as a donor of Galactose units in many biosynthetic reactions:

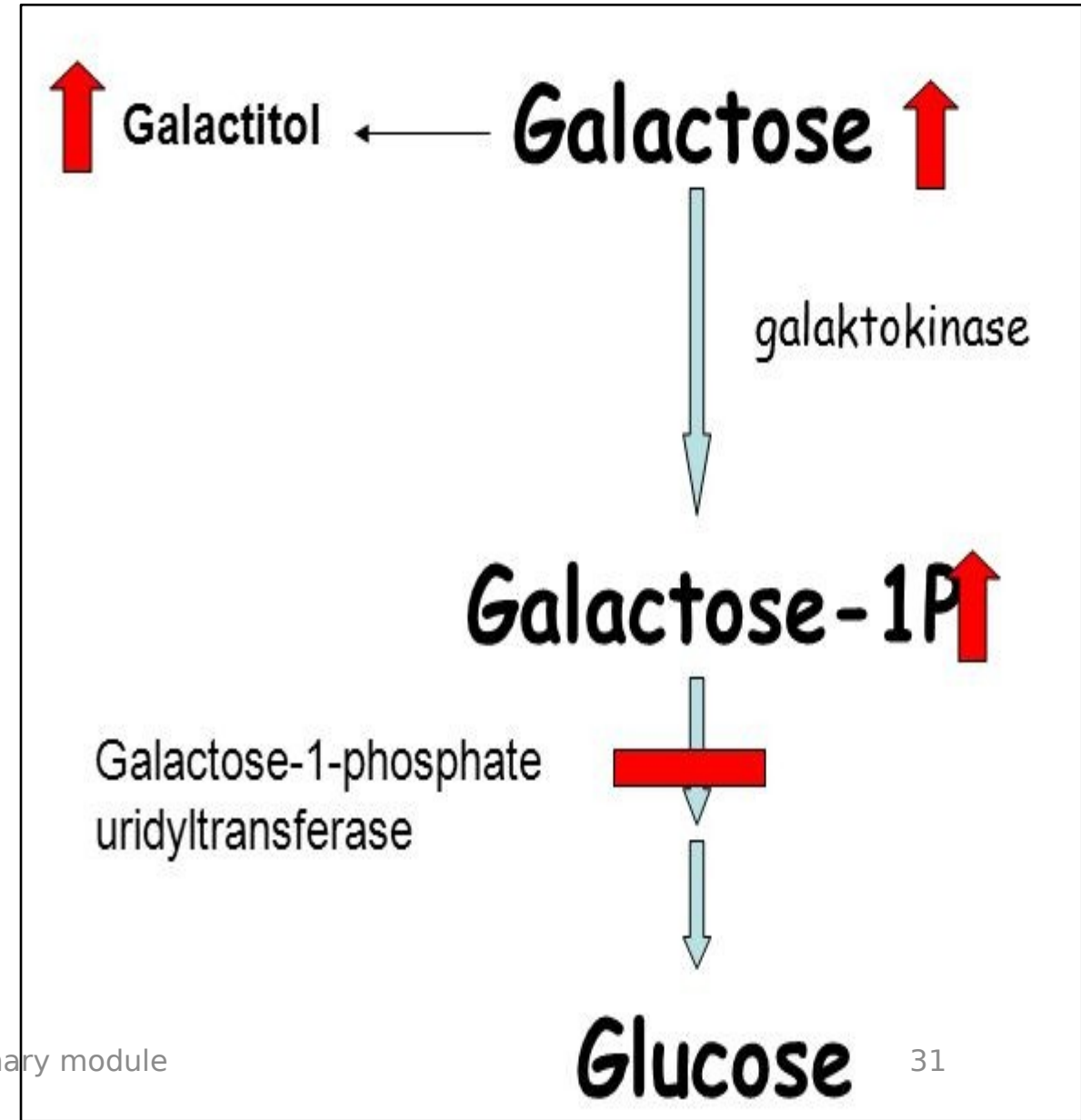


1. **Glycolipids.**
2. **Glycoproteins.**
3. **Lactose (milk sugar) produced by mammary glands during lactation**

GALACTOSEMIA

1- Classic galactosemia (Sever form)

- **Inborn error of galactose metabolism**
- **Due to deficiency of Galactose-1-p uridyl Transferase (GALT) enzyme**
- **Galactose 1-phosphate and, galactose accumulate in cells**



Clinical picture of classic galactosemia

Symptoms start at first days after breast feeding

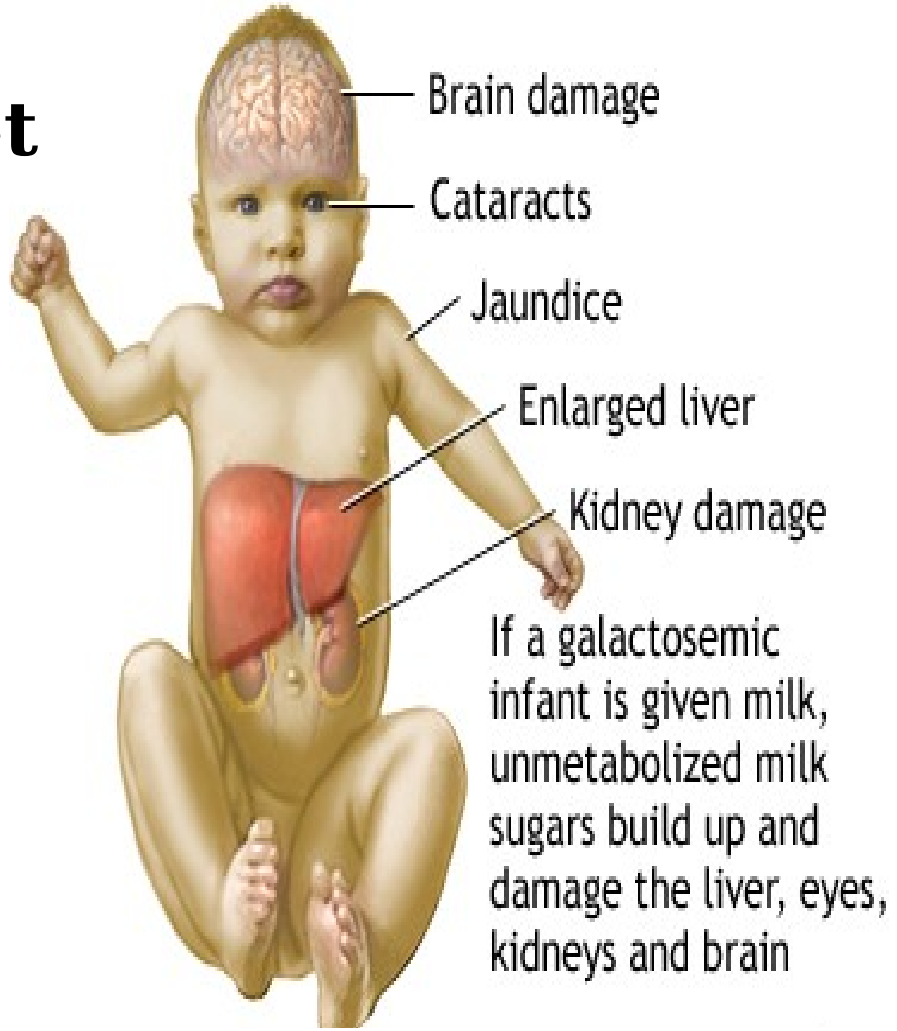
1- Accumulation of Galactose-1-phosphate and depletion of liver inorganic phosphate ⟹ Hypoglycemia and vomiting

2- Galactose is a substrate for aldose reductase, forming galactitol, which accumulates in:

- **Lens of the eye ⟹ Cataract**
- **Nerves ⟹ Mental Retardation**
- **Liver ⟹ Liver failure & jaundice**
- **Kidney ⟹ Renal failure**

Treatment of classic galactosemia

- **The only treatment is eliminating lactose and galactose from the diet**
- **Infants cannot be breast-fed and are usually fed a soy-based**



2- Galactokinase deficiency (Mild form)

It is a mild disorder of galactosemia

excess galactose

↓ aldose reductase

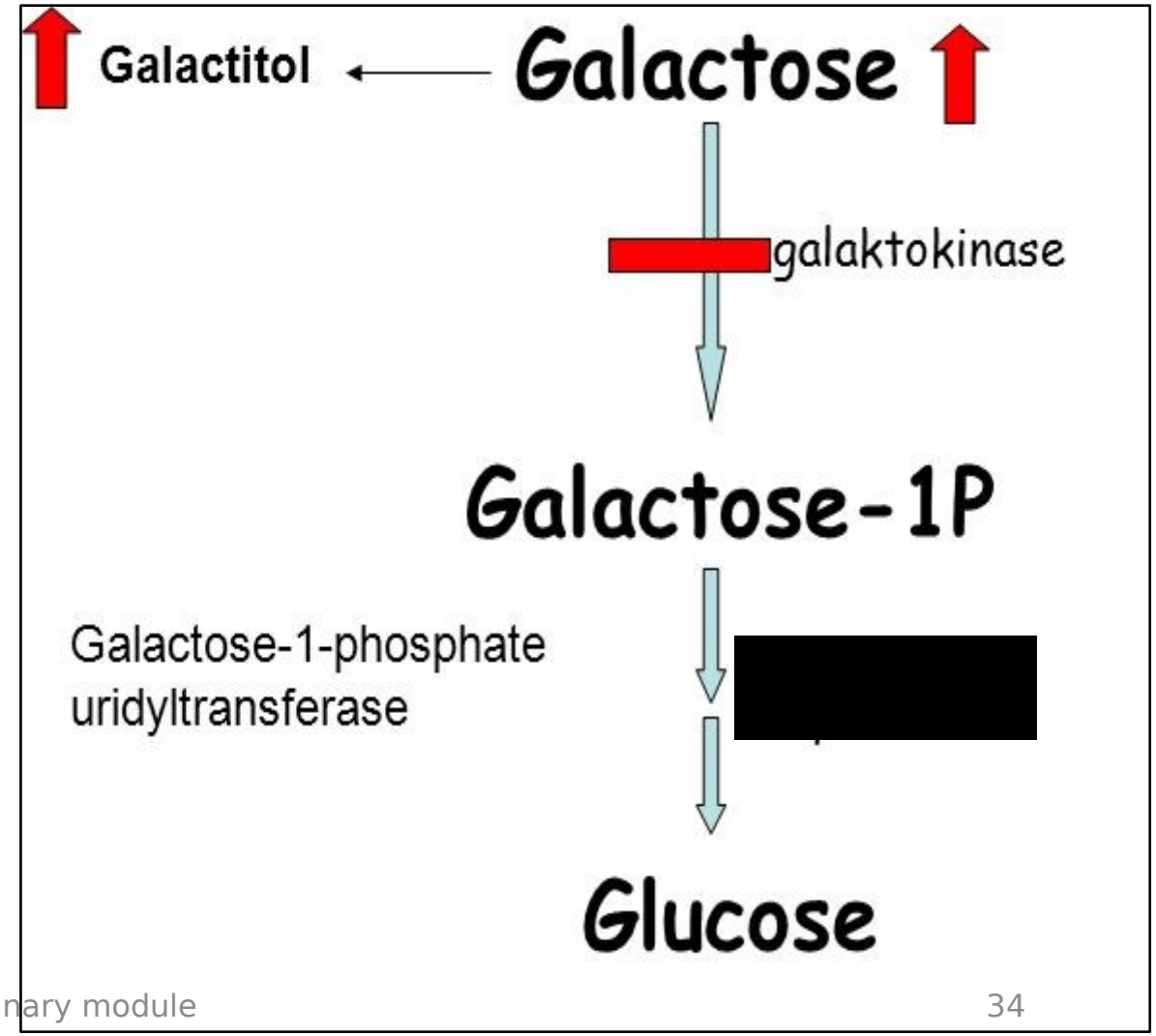
formation of galactitol

↓

accumulates in the lens of the eye

↓

producing cataract.

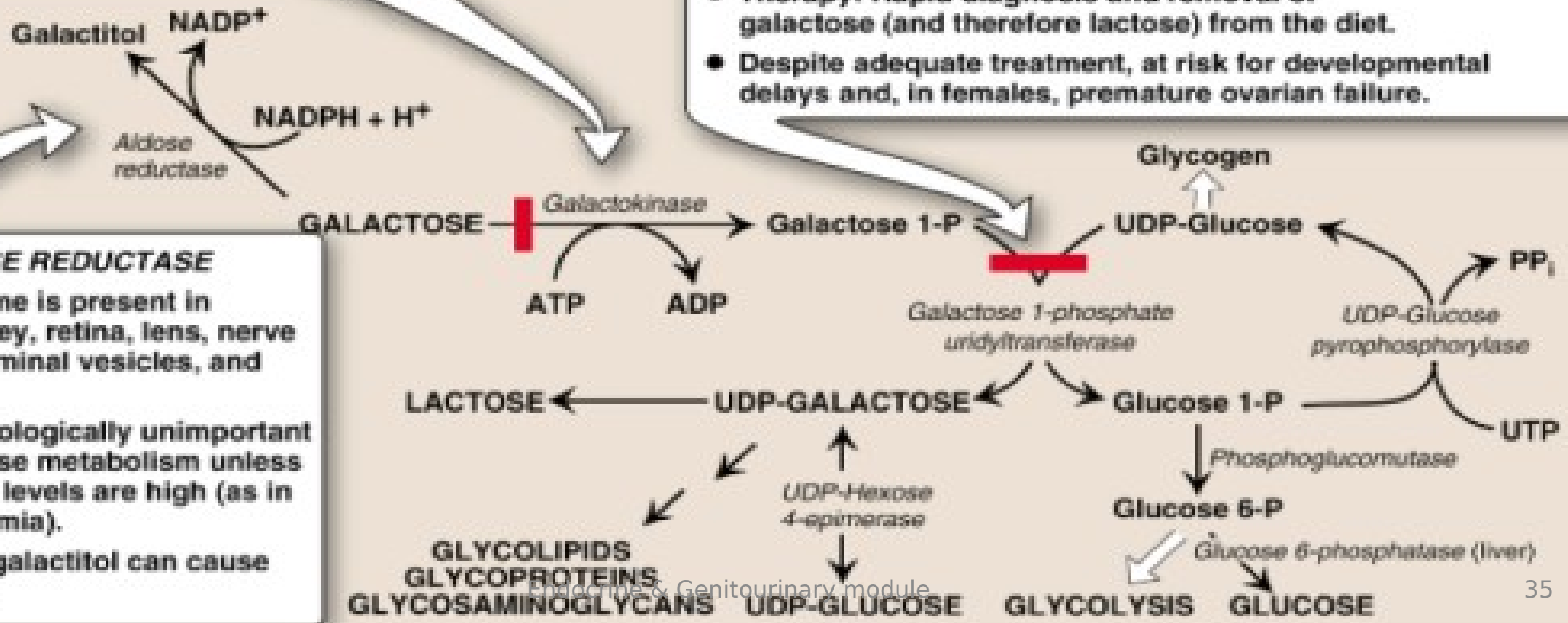


GALACTOKINASE DEFICIENCY

- Rare autosomal recessive disorder
- Causes elevation of galactose in blood (galactosemia) and urine (galactosuria)
- Causes galactitol accumulation if galactose is present in the diet.
- Elevated galactitol can cause cataracts.
- Treatment is dietary restriction.

CLASSIC GALACTOSEMIA

- *Galactose 1-phosphate uridyltransferase* (*GALT*) deficiency.
- Autosomal recessive disorder (1:30,000 births).
- Causes galactosemia and galactosuria, vomiting, diarrhea, and jaundice.
- Accumulation of galactose 1-phosphate and galactitol in nerve, lens, liver, and kidney tissue causes liver damage, severe mental retardation, and cataracts.
- Prenatal diagnosis is possible by chorionic villus sampling. Newborn screening is available.
- Therapy: Rapid diagnosis and removal of galactose (and therefore lactose) from the diet.
- Despite adequate treatment, at risk for developmental delays and, in females, premature ovarian failure.



ALDOSE REDUCTASE

- The enzyme is present in liver, kidney, retina, lens, nerve tissue, seminal vesicles, and ovaries.
- It is physiologically unimportant in galactose metabolism unless galactose levels are high (as in galactosemia).
- Elevated galactitol can cause cataracts.

The…… utilize fructose but not glucose.

(a)Ovum
(b)Spermatozoa
(c) Adipose tissue
(d)Mammary gland

Which enzyme is deficient in the liver in cases of hereditary fructose intolerance?

1. Hexokinase
2. Aldolase B
3. Glucokinase
4. Phosphofructokinase
5. Triose kinase

Hexokinase has a considerably lower km and very high affinity for?

a) Glucose
b) Fructose
c) Sucrose
d) Mannose
e) lactose

In classic galactosemia , there is deficiency of

1. **Galactosidase**
2. **Galactose 1-phosphate uridyl transferase**
3. **Aldolase reductase**
4. **UDP-Hexose 4 epimerase**

Which of the following statements about galactose is correct?

1. Galactose cannot be metabolised and remains in our blood after we consume milk.
2. Galactose is a glucose epimer that can be used as a substrate by the enzymes that use glucose as a substrate.
3. Galactose and fructose can easily be interconverted.
4. Galactosaemia is a serious genetic disease that requires the removal of galactose from the diet of newborn infants

Galactose-1-P uridyl Transferase deficiency will leads to accumulation of:

1. galactose 1 Phosphate.
2. glucose 6 Phosphate. .
3. glycogen.
4. UTP.

Galactosemia may be treated most practically by:

1. Adopting a high-carbohydrate diet.
2. Eliminating all sugar from the diet.
3. Excluding milk & milk products from the diet.
4. Adopting a high-protein diet.
5. Avoiding the use of sucrose.

Thank you

Marwa Ali